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Primary Pulmonary Rhabdomyosarcoma in Childhood: Clinico-Biologic Features in Two Cases With Review of the Literature

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The cases of two children under three years of age with primary pulmonary rhabdomyosarcoma and no associated lung malformations are reported and a review of the literature is presented. In both, complete surgical removal of the tumor was performed and histologic examination revealed embryonal subtype. Flow cytometric assessment showed a tumor-cell diploid DNA content. Postoperative radio- and chemotherapy were carried out, but in spite of treatment both girls died because of disease progression, fourteen and nine months after diagnosis. The importance of associated cystic lung malformations and DNA content in predicting clinical outcome of primary pulmonary rhabdomyosarcoma is evaluated.

Key words: rhabdomyosarcoma, lung tumors, DNA ploidy

INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma in children, representing 5% to 8% of all childhood malignancies. RMS may arise in any site, even where striated muscle is not normally present. The most common localizations are the head and neck, the genitourinary tract, the extremities and the trunk [1].

Primary pulmonary RMS is extremely rare, with 18 cases reported in the literature so far [2–12]. Most develop within preexisting cystic lesions or are of endobronchial origin. The clinical and biologic features of two cases of primary pulmonary RMS are reported here.

CASE 1

A 30-month-old girl was admitted to our department because of a persistent cough, without fever, which arose four months earlier. A chest X-ray (Fig. 1) showed a density involving the right lung with a contralateral deviation of the mediastinum. Additional diagnostic investigations, including a neurologic examination, were negative. The child underwent surgery that revealed a tumor mass in the superior lobe of the right lung; a superior lobectomy was then performed with complete removal of the tumor. Histologic examination showed an embryonal RMS and, since no other locations were involved, a diagnosis of primary pulmonary RMS was made. Radiotherapy was administered to the right hemithorax for a total dose of 2,000 cGys. Chemotherapy with cyclophosphamide and vincristine was administered but fourteen months after diagnosis distant recurrence with brain metastases occurred during chemotherapy and the child died.

Pathologic Examination

The resected mass (15 × 10 × 10 cm) was irregularly oval in shape and reddish-gray in color; the cut surface showed many hemorrhagic and necrotic areas. Histologic examination demonstrated the presence of bundles of spindle-shaped cells with hyperchromatic nuclei and ill-defined cytoplasmic boundaries. Large, round or spindle-shaped cells with abundant, intensely eosinophilic cytoplasm, and with intensely stained monstrous nuclei, intermixed with areas of myxoid tissues, were present. There were also many abnormal mitoses. Tumor tissue was continuous with the lung alveolar structures, with no interposition of dividing collagenous septa. Phosphotungstinic acid-hematoxylin (PTAH) staining showed cross-striations in some cells. A diagnosis of pulmonary embryonal RMS was made.

Biologic Features

Flow cytometric measurement of cellular DNA content (DNA ploidy) was carried out on paraffin-embedded

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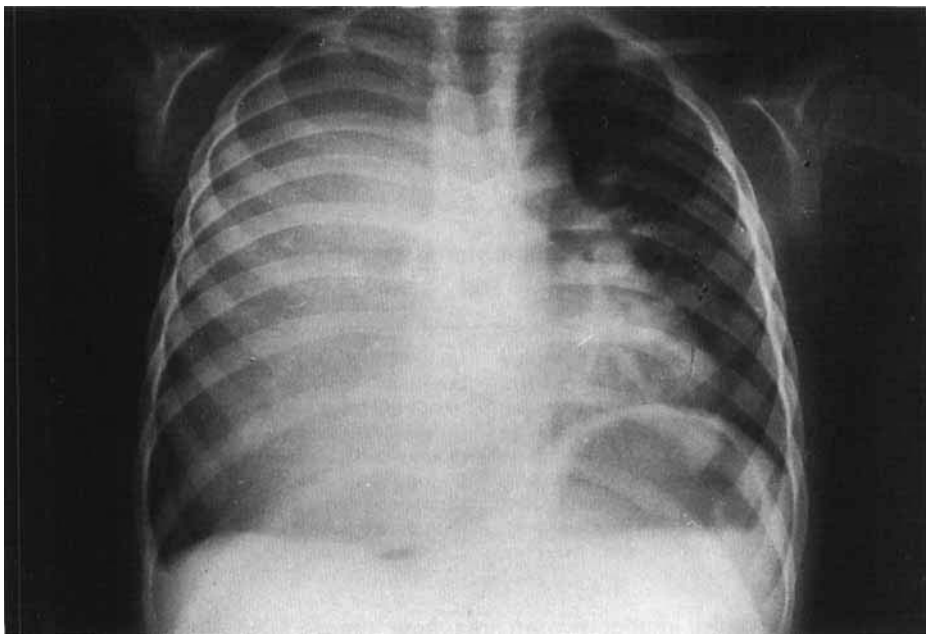

Fig. 1. In case 1, a chest X-ray shows a density in the right hemithorax with inferior displacement of the right main bronchus and dislocation of the heart and mediastinum to the left.

tumor tissue according to Hedley et al. [13]. Ploidy was defined as follows: diploidy by a DNA index (DI) range of 0.9 to 1.1; triploidy by a DI of 1.2 to 1.8; and tetraploidy by a DI of 1.9 to 2.2 [14,15]. In this case, tumor-cell DNA ploidy was diploid.

CASE 2

An 18-month-old girl was admitted to our department because of cough, fever, dyspnea, and compulsatory right decubitus. A chest X-ray (Fig. 2) demonstrated a density in the right lower lobe. Pneumonia was suspected and the child was treated with broad-spectrum antibiotics. Due to the worsening conditions, a total body CT scan (Fig. 3) was carried out, and this showed a mass in the right lung. No other lesions were seen and all additional diagnostic examinations were negative. The girl underwent an open surgical biopsy, and a right lower lobectomy with complete tumor removal was performed. Histologic examination demonstrated a RMS and therefore a diagnosis of primary pulmonary RMS was made. Postoperative chemotherapy was carried out according to the Italian Protocol for RMS (RMS 87 AIEOP) which includes ifosphamide, actinomycin-D, and vincristine. Two months after surgery and during chemotherapy, a chest X-ray and a subsequent CT scan (Fig. 4) demonstrated a local relapse. A second operation was performed with macroscopically complete tumor resection. Postoperative radiotherapy was carried out but the child died a month later because of a second local relapse.

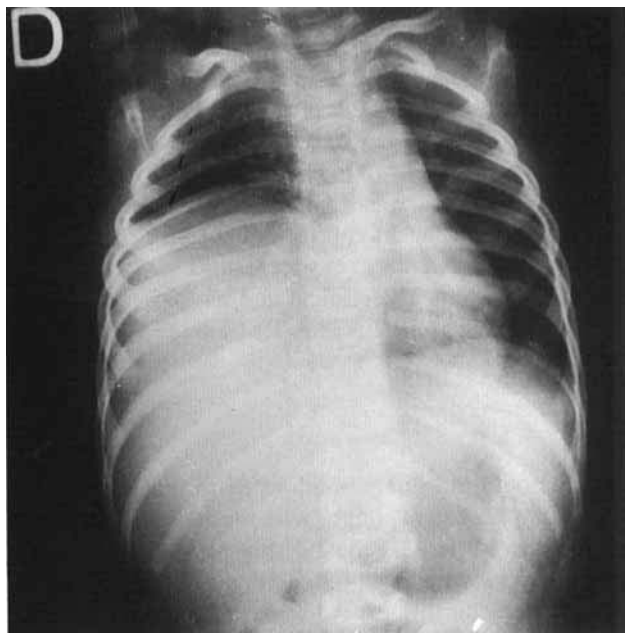

Fig. 2. In case 2, a chest X-ray shows a density in the right lower lobe with mediastinal displacement.

Pathologic Examination

The mass resected at the first operation (13 × 12 × 9 cm) was grayish in color with an encephaloid-like cut surface disseminated with necrotic areas. Histologic examination showed tumor tissue containing polymorphic and polymetric cells with hyperchromatic and in some

Fig. 3. In case 2, a contrast-enhanced CT scan at diagnosis shows a huge nonhomogeneous lung mass in the right hemithorax extending to the chest wall.

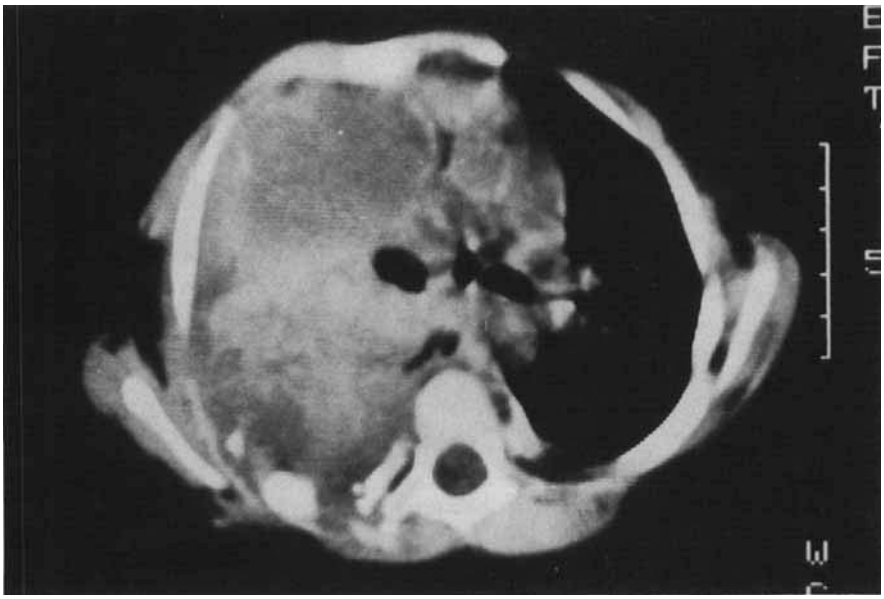

Fig. 4. In case 2, a CT scan at the first relapse shows a recurrent soft-tissue mass invading the mediastinum and extending to the chest wall.

cases monstrous and bizarre nuclei; numerous abnormal mitoses were present. There was a great amount of myxoid tissue. Also, in this case no interposition of dividing collagenous septa between tumor and lung alveolar tissue was recognizable (Figs. 5, 6). PTAH staining showed cross-striations in some tumor cells. Immunohistochemical examination with immunoperoxidase technique demonstrated specific immunoreactivity for desmin and myoglobin. A diagnosis of embryonal pulmonary RMS was made.

Biologic Features

Also in this case, flow cytometric assessment demonstrated a diploid tumor-cell DNA content.

DISCUSSION

Primary pulmonary RMS represents an extremely rare neoplasm in childhood [16], only 18 cases of which have been reported so far [2–12] (Table I). Only three of the

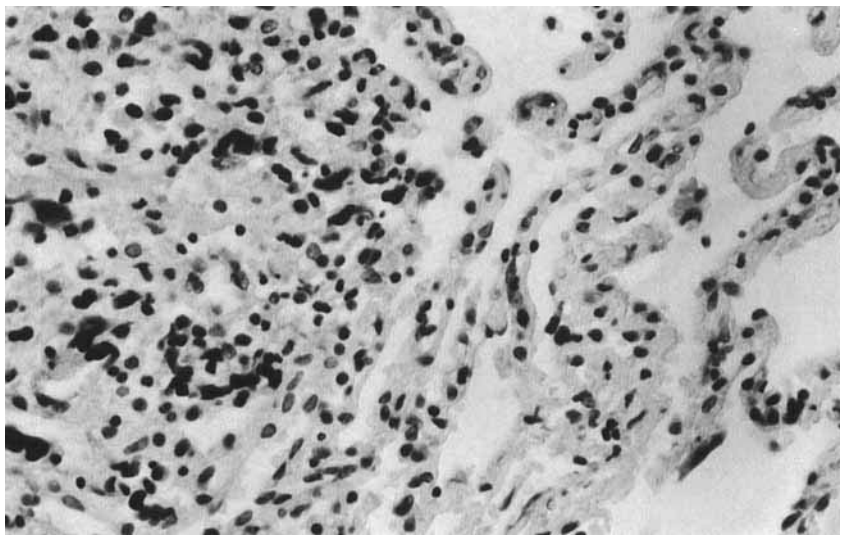

Fig. 5. Neoplastic cells invading lung alveoli. Hematoxylin and eosin, ×100.

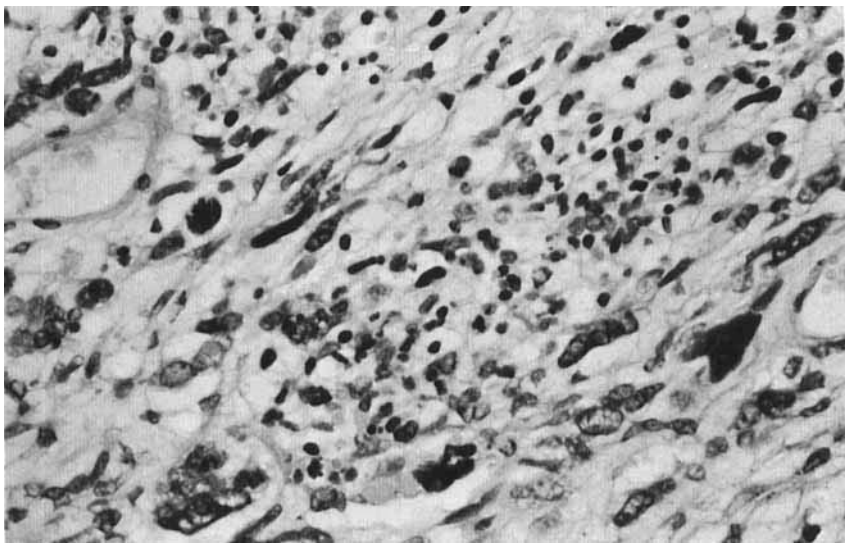

Fig. 6. Tumor tissue with anaplastic elements. Hematoxylin and eosin, ×200.

646 children included in the Intergroup Rhabdomyosarcoma Study (IRS) had a primary pulmonary lesion [3,17]. Murphy et al. recently reported three cases [8]; Allan et al. [2], Hartman and Shochat [5], and Hedlund et al. [6] each described two, while other case reports concerned only one patient each [4,7,9–12]. At our department we observed two cases of pulmonary RMS 16 years apart: in 1970 and in 1986.

The most common symptoms at onset are cough and fever, followed by spontaneous pneumothorax. In our cases, both arising in two girls less than three years of age, the symptoms were persistent cough in both, and fever and dyspnea only in the second.

In both patients the tumor originated from normal lung tissue. Among the 18 cases of primary pulmonary RMS so far published, eight were related to preexisting pulmonary cystic lesions [6–9,11], four originated from the bronchial wall [4,5,10], and six were described without specifying the possible associated pulmonary lesions.

Regarding the histogenesis of pulmonary RMS, two hypotheses have been proposed [18]. The first states that the tumor arises from heterotopic islets of striated muscle, thus explaining the frequent association of RMS with pulmonary malformations such as bronchogenic cysts and cystic adenomatosis where these islets are present [19,20]. This association once again raises the more gen-

TABLE I. Primary Pulmonary Rhabdomyosarcoma: Review of the Literature

Patients	Sex/age (months)	Stage	Histology	Symptoms	Associated lung cyst	Therapy	Outcome follow-up	Reference
2	F/30	I or II	Not specified	PNX[f]	Uncertain	S[h] + CHT[b]	AWD[a] 11 mos (Local relapse after 5 mos)	[2]
	F/21	I	Not specified	PNX	Uncertain	S + CHT	NED[e] 48 mos	
3	F/156	IV	Alveolar	Not specified	Not specified	CHT + RT[g]	DOD[c] 16 mos	
	M/168	II	Undifferentiated	Not specified	Not specified	S + CHT + RT	NED 72 mos	[3]
	M/84	I	Undifferentiated	Not specified	Not specified	S + CHT + RT	LTF[d]	
1	F/72	III	Embryonal	Fever	No	S + CHT + RT	AWD 33 mos	[4]
2	M/122	I or II	Not specified	Cough, Fever	No	S + CHT + RT	NED 24 mos	
	F/156	I or II	Embryonal	Cough, Pain	No	S + CHT + RT	AWD 12 mos (Distant relapse after 48 mos)	[5]
1	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	[12]
2	F/22	I or II	Not specified	Dyspnea	Yes	S + CHT	NED 9 mos	
	F/18	I or II	Embryonal	Croup	Yes	S + CHT	NED 12 mos	[6]
1	F/30	III	Embryonal	Cough, Fever	Yes	S + CHT + RT	DOD 6 mos	[7]
3	F/24	II	Embryonal	PNX	Yes	S + CHT	NED 24 mos	
	F/36	II	Embryonal	PNX	Yes	S + CHT	NED 3 mos	[8]
	M/42	II	Not specified	Fever, Cough	Yes	S + CHT	NED 6 mos	
1	F/15	I or II	Not specified	Cough, Fever	Yes	S	NED 3 mos	[9]
1	M/21	I or II	Embryonal	Cough, Pain	No	S + CHT	NED 60 mos	[10]
1	F/18	I	Embryonal	Fever, Cough	Yes	S + CHT	NED 41 mos	[11]
2	F/30	II	Embryonal	Cough	No	S + CHT + RT	DOD 14 mos	
	F/18	II	Embryonal	Fever, Cough, Dyspnea	No	S + CHT + RT	DOD 9 mos	This study

[a]AWD: Alive with disease.
[b]CHT: Chemotherapy.
[c]DOD: Dead of disease.
[d]LTF: Lost to follow-up.
[e]NED: No evidence of disease.
[f]PNX: Pneumothorax.
[g]RT: Radiotherapy.
[h]S: Surgery.

eral question concerning the relationship between teratogenesis and oncogenesis [21]. The second hypothesis, which seems more appropriate for those cases not related to preexisting cystic lesions, suggests a neoplastic transformation of the uncommitted mesenchymal cells present in the interstitial lung tissue or bronchioli [22].

These pathogenetic hypotheses could be related to clinico-biologic tumor behavior. Although in the case reports published so far the follow-ups are limited, from the analysis of all the primary pulmonary RMSs reported so far, there seems to be a difference in disease-free survival rate between those tumors associated with cystic lesions and those without. In fact, of the eight cases with associated cystic lesions, seven are disease-free and one is dead of disease; while in the eleven cases without detectable lung cysts four are free of disease, three alive with disease, three dead of disease, and one lost to follow-up.

Many prognostic factors have been described in childhood RMS such as clinical group and extent of disease at diagnosis, primary site, histologic subtype, and even early response to treatment [23]. Both our patients underwent complete surgical resection and were diagnosed as belonging to clinical group II. The percentage of 5-year survivors in this group is approximately 70% [24]. In both cases the histologic diagnosis was embryonal RMS, the subtype reported to have a more favorable prognosis than alveolar RMS in overall survival rate, but not necessarily in disease-free survival [24]. Both patients underwent postoperative chemotherapy and local radiotherapy. Nevertheless, the tumors rapidly progressed and both patients died during treatment, the first at 14 months after diagnosis because of distant recurrence, and the second at nine months after diagnosis due to a second local relapse.

In these two cases, flow cytometric evaluation of DNA content was carried out on paraffin-embedded tumor tissue in order to retrospectively identify markers possibly associated with their aggressive behavior. Previous studies have demonstrated that in RMS, tumor-cell DNA ploidy identifies subsets of patients with significantly different risks of relapse and death, even within the same histologic subtype [25,26]. Our findings are in agreement with those previously reported which showed that diploid cases present a more aggressive behavior than triploid or tetraploid ones [25,26].

In conclusion, primary pulmonary RMS, although very rare, should be considered in the differential diagnosis of childhood lung masses, and the simultaneous presence of cystic lesions could be considered as a favorable prognostic feature.

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